Rheumatology Suggested Reading List

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Rheumatoid Arthritis:

- 1994: Elliott, Michael J., et al. "Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis." *The Lancet* 344.8930 (1994): 1105-1110.
    - The results provide the first good evidence that specific cytokine blockade can be effective in human inflammatory disease and define a new direction for the treatment of rheumatoid arthritis.
- 2000: Bathon, Joan M., et al. "A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis." *New England Journal of Medicine* 343.22 (2000): 1586-1593.
    - As compared with oral methotrexate, subcutaneous etanercept acted more rapidly to decrease symptoms and slow joint damage in patients with early active rheumatoid arthritis.
- 2002: Choi, Hyon K., et al. "Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study." *The Lancet* 359.9313 (2002): 1173-1177.
    - Methotrexate may provide a substantial mortality benefit, likely by reducing cardiovascular risk.
- 2004: Edwards, Jonathan CW, et al. "Efficacy of B-cell–targeted therapy with rituximab in patients with rheumatoid arthritis." *New England Journal of Medicine* 350.25 (2004): 2572-2581.
    - In patients with active rheumatoid arthritis despite methotrexate treatment, a single course of two infusions of rituximab, alone or in combination with either cyclophosphamide or continued methotrexate, provided significant improvement in disease symptoms at both weeks 24 and 48.

- 2004: Grigor, Catriona, et al. "Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial." *The Lancet* 364.9430 (2004): 263-269.
    - **TICORA** study: A strategy of intensive outpatient management of rheumatoid arthritis substantially improves disease activity, radiographic disease progression, physical function, and quality of life at no additional cost.
- 2005: Goekoop-Ruiterman, Y. P. M., et al. "Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial." *Arthritis & Rheumatism* 52.11 (2005): 3381-3390.
    - **BeSt** trial – in early RA, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage at 1 year than did sequential monotherapy or step-up combination therapy
- 2005: Genovese, Mark C., et al. "Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition." *New England Journal of Medicine* 353.11 (2005): 1114-1123.
    - Abatacept produced significant clinical and functional benefits in patients who had had an inadequate response to anti–TNF-α therapy.
- 2006: Baecklund, Eva, et al. "Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis." *Arthritis & Rheumatism* 54.3 (2006): 692-701.
    - Risk of lymphoma is substantially increased in a subset of patients with RA, those with very severe disease. High inflammatory activity, rather than its treatment, is a major risk determinant.
- 2008: Smolen, Josef S., et al. "Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial." *The Lancet* 371.9617 (2008): 987-997.
    - **OPTION** study: Tocilizumab could be an effective therapeutic approach in patients with moderate to severe active rheumatoid arthritis.

- 2008: Emery, Paul, et al. "Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial." *The Lancet* 372.9636 (2008): 375-382.
    - **COMET** trial: Both clinical remission and radiographic non-progression are achievable goals in patients with early severe rheumatoid arthritis within 1 year of combined treatment with etanercept plus methotrexate.
- 2012: Fleischmann, Roy, et al. "Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis." *New England Journal of Medicine* 367.6 (2012): 495-507.
    - In patients with active rheumatoid arthritis, tofacitinib monotherapy was associated with reductions in signs and symptoms of rheumatoid arthritis and improvement in physical function
- 2013: O'dell, James R., et al. "Therapies for active rheumatoid arthritis after methotrexate failure." *New England Journal of Medicine* 369.4 (2013): 307-318.
    - With respect to clinical benefit, triple therapy, with sulfasalazine and hydroxychloroquine added to methotrexate, was noninferior to etanercept plus methotrexate in patients with rheumatoid arthritis who had active disease despite methotrexate therapy.

Gout:

- 2004: Borstad, Gregory C., et al. "Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis." *The Journal of Rheumatology* 31.12 (2004): 2429-2432.
    - Colchicine prophylaxis during initiation of allopurinol for chronic gouty arthritis reduces the frequency and severity of acute flares, and reduces the likelihood of recurrent flares. Treating patients with colchicine during initiation of allopurinol therapy for 6 months is supported.
- 2008: Schumacher, H. RALPH, et al. "Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A

28-week, phase III, randomized, double-blind, parallel-group trial." *Arthritis Care & Research* 59.11 (2008): 1540-1548.

  - At all doses studied, febuxostat more effectively lowered and maintained serum urate levels <6.0 mg/dl than did allopurinol (300 or 100 mg) or placebo in subjects with hyperuricemia and gout, including those with mild to moderately impaired renal function.

- 2010: Becker, Michael A., et al. "The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial." *Arthritis research & therapy* 12.2 (2010): R63.
  - **CONFIRMS** trial: Urate-lowering efficacy of febuxostat 80 mg exceeded that of febuxostat 40 mg and allopurinol (300/200 mg), which were comparable. In subjects with mild/moderate renal impairment, both febuxostat doses were more efficacious than allopurinol and equally safe. At the doses tested, safety of febuxostat and allopurinol was comparable.

Ankylosing spondylitis:

- 1996: Clegg, Daniel O., et al. "Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis. A Department of Veterans Affairs Cooperative Study." *Arthritis & Rheumatism* 39.12 (1996): 2004-2012.
  - SSZ at a dosage of 2,000 mg/day does not seem to be more effective than placebo in the treatment of AS patients with chronic, longstanding disease. SSZ is well tolerated and may be more effective than placebo in the treatment of AS patients with peripheral joint involvement. This effect is more pronounced in treatment of the peripheral arthritis in this subgroup of AS patients.
- 2002: Braun, J., et al. "Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial." *The Lancet* 359.9313 (2002): 1187-1193.
  - Treatment with infliximab is effective in patients with active ankylosing spondylitis

- 2015: Baeten, Dominique, et al. "Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis." *New England Journal of Medicine* 373.26 (2015): 2534-2548.
    - **MEASURE**: Secukinumab at a subcutaneous dose of 150 mg, with either subcutaneous or intravenous loading, provided significant reductions in the signs and symptoms of ankylosing spondylitis at week 16. Secukinumab at a subcutaneous dose of 75 mg resulted in significant improvement only with a higher intravenous loading dose

Psoriatic Arthritis:

- 2013: McInnes, Iain B., et al. "Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial." *The Lancet* 382.9894 (2013): 780-789.
    - **PSUMMIT**: Ustekinumab significantly improved active psoriatic arthritis compared with placebo, and might offer an alternative therapeutic mechanism of action to approved biological treatments.
- 2014: Kavanaugh, Arthur, et al. "Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor." *Annals of the rheumatic diseases* 73.6 (2014): 1020-1026.
    - **PALACE1**: Apremilast was effective in the treatment of psoriatic arthritis, improving signs and symptoms and physical function. Apremilast demonstrated an acceptable safety profile and was generally well tolerated.
- 2015: McInnes, Iain B., et al. "Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial." *The Lancet* 386.9999 (2015): 1137-1146.
    - **FUTURE2**: Subcutaneous secukinumab 300 mg and 150 mg improved the signs and symptoms of psoriatic arthritis, suggesting that secukinumab is a potential future treatment option for patients with this disorder.

Scleroderma:

- 1979: Lopez-Ovejero, Jorge A., et al. "Reversal of vascular and renal crises of scleroderma by oral angiotensin-converting-enzyme blockade." *New England Journal of Medicine* 300.25 (1979): 1417-1419.
    - This describes the first successful treatment of SRC with ACE inhibitors.
- 2000: Steen, Virginia D., and Thomas A. Medsger. "Long-term outcomes of scleroderma renal crisis." *Annals of Internal Medicine* 133.8 (2000): 600-603.
    - Renal crisis can be effectively managed when hypertension is aggressively controlled with ACE inhibitors. Patients should continue taking ACE inhibitors even after beginning dialysis in hopes of discontinuing dialysis.
- 2006: Tashkin, Donald P., et al. "Cyclophosphamide versus placebo in scleroderma lung disease." *New England Journal of Medicine* 354.25 (2006): 2655-2666.
    - **Scleroderma Lung Study**: One year of oral cyclophosphamide in patients with symptomatic scleroderma-related interstitial lung disease had a significant but modest beneficial effect on lung function, dyspnea, thickening of the skin, and the health-related quality of life. The effects on lung function were maintained through the 24 months of the study.
- 2016: Tashkin, Donald P., et al. "Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial." *The Lancet Respiratory Medicine* 4.9 (2016): 708-719.
    - **Scleroderma Lung Study II**: Treatment of scleroderma-related interstitial lung disease with mycophenolate mofetil for 2 years or cyclophosphamide for 1 year both resulted in significant improvements in prespecified measures of lung function over the 2 year course of the study. Although mycophenolate mofetil was better tolerated and associated with less toxicity, the hypothesis that it would have greater efficacy at 24 months than cyclophosphamide was not confirmed. These findings support the potential

clinical effectiveness of both cyclophosphamide and mycophenolate mofetil for progressive scleroderma-related interstitial lung disease, and the present preference for mycophenolate mofetil because of its better tolerability and toxicity profile.

Systemic Lupus Erythematosus:

- 1991: The Canadian Hydroxychloroquine Study Group. "A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus." *N Engl j Med* 324 (1991): 150-4.
    - Patients with quiescent SLE who are taking hydroxychloroquine are less likely to have a clinic flare-up if they are maintained on the drug.
- 1992: Boumpas, Dimitrios T., et al. "Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis." *The Lancet* 340.8822 (1992): 741-745.
    - An extended course of pulse cyclophosphamide is more effective than 6 months of pulse methylprednisolone in preserving renal function in patients with severe lupus nephritis. Addition of a quarterly maintenance regimen to monthly pulse cyclophosphamide reduces the rate of exacerbations.
- 2004: Contreras, Gabriel, et al. "Sequential therapies for proliferative lupus nephritis." *New England Journal of Medicine* 350.10 (2004): 971-980.
    - For patients with proliferative lupus nephritis, short-term therapy with intravenous cyclophosphamide followed by maintenance therapy with mycophenolate mofetil or azathioprine appears to be more efficacious and safer than long-term therapy with intravenous cyclophosphamide.
- 2005: Buyon, Jill P., et al. "The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial." *Annals of internal medicine* 142.12_Part_1 (2005): 953-962.

    - **SELENA**: Hormone replacement therapy given for 1 year does not significantly increase the risk for severe flare but does increase the risk for mild to moderate flares in menopausal women with SLE
- 2005: Ginzler, Ellen M., et al. "Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis." *New England Journal of Medicine* 353.21 (2005): 2219-2228.
    - In this 24-week trial, mycophenolate mofetil was more effective than intravenous cyclophosphamide in inducing remission of lupus nephritis and had a more favorable safety profile.
- 2007: Alarcón, Graciela S., et al. "Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L)." *Annals of the rheumatic diseases* 66.9 (2007): 1168-1172.
    - **LUMINA**: Hydroxychloroquine, which overall is well tolerated by patients with SLE, has a protective effect on survival which is evident even after taking into consideration the factors associated with treatment decisions. This information is of importance to all clinicians involved in the care of patients with SLE.
- 2010: Merrill, Joan T., et al. "Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial." *Arthritis & Rheumatism* 62.1 (2010): 222-233.
    - **EXPLORER**: Enrolled patients with moderately-to-severely active SLE and used aggressive background treatment and sensitive cutoffs for nonresponse. No differences were noted between placebo and rituximab in the primary and secondary end points. Further evaluation of patient subsets, biomarkers, and exploratory outcome models may improve the design of future SLE clinical trials.
- 2010: Houssiau, Frédéric A., et al. "Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial." *Annals of the rheumatic diseases* 69.12 (2010): 2083-2089.

    - **MAINTAIN** trial: Tested whether MMF was superior to azathioprine for maintenance therapy. Fewer renal flares were observed in patients receiving MMF but the difference did not reach statistical significance.
- 2011: Furie, Richard, et al. "A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus." *Arthritis & Rheumatism* 63.12 (2011): 3918-3930.
    - Belimumab plus standard therapy significantly improved SRI response rate, reduced SLE disease activity and severe flares, and was generally well tolerated in SLE
- 2011: Dooley, Mary Anne, et al. "Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis." *New England Journal of Medicine* 365.20 (2011): 1886-1895.
    - **ALMS** trial: Mycophenolate mofetil was superior to azathioprine in maintaining a renal response to treatment and in preventing relapse in patients with lupus nephritis who had a response to induction therapy
- 2012: Rovin, Brad H., et al. "Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study." *Arthritis & Rheumatism* 64.4 (2012): 1215-1226.
    - **LUNAR** trial: Although rituximab therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels, it did not improve clinical outcomes after 1 year of treatment. The combination of rituximab with MMF and corticosteroids did not result in any new or unexpected safety signals.

Myositis:

- 1993: Dalakas, Marinos C., et al. "A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis." *New England Journal of Medicine* 329.27 (1993): 1993-2000.

    - High dose IVIG is a safe and effective treatment for refractory dermatomyositis.
- 2013**:** Oddis, Chester V., et al. "Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: A randomized, placebo-phase trial." *Arthritis & Rheumatism* 65.2 (2013): 314-324.
    - Although there were no significant differences in the two treatment arms for the primary and secondary endpoints, 83% of refractory adult and juvenile myositis patients met the DOI. The role of B cell depleting therapies in myositis warrants further study with consideration for a different trial design.

Vasculitis:

- 1983: Fauci, Anthony S., et al. "Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years." *Annals of internal medicine* 98.1 (1983): 76-85.
    - This study provides a prospective experience with Wegener's granulomatosis and shows that long-term remissions can be induced and maintained in an extremely high number of patients by the combination of daily cyclophosphamide and alternate-day prednisone therapy.
- 2003: Jayne, David, et al. "A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies." *New England Journal of Medicine* 349.1 (2003): 36-44.
    - In patients with generalized vasculitis, the withdrawal of cyclophosphamide and the substitution of azathioprine after remission did not increase the rate of relapse. Thus, the duration of exposure to cyclophosphamide may be safely reduced.
- 2009: de Groot, Kirsten, et al. "Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody—Associated VasculitisA Randomized Trial." *Annals of internal medicine* 150.10 (2009): 670-680.

    - **CYCLOPS** study: The pulse cyclophosphamide regimen induced remission of ANCA-associated vasculitis as well as the daily oral regimen at a reduced cumulative cyclophosphamide dose and caused fewer cases of leukopenia.
- 2010: Stone, John H., et al. "Rituximab versus cyclophosphamide for ANCA-associated vasculitis." *New England Journal of Medicine* 363.3 (2010): 221-232.
    - **RAVE** trial: Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis and may be superior in relapsing disease
- 2010: Jones, Rachel B., et al. "Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis." *New England Journal of Medicine* 363.3 (2010): 211-220.
    - **RITUXVAS**: A rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis. Sustained-remission rates were high in both groups, and the rituximab-based regimen was not associated with reductions in early severe adverse events
- 2014: Guillevin, Loïc, et al. "Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis." *New England Journal of Medicine* 371.19 (2014): 1771-1780.
    - More patients with ANCA-associated vasculitides had sustained remission at month 28 with rituximab than with azathioprine.

Sjogrens:

- 2014: Gottenberg, Jacques-Eric, et al. "Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial." *Jama* 312.3 (2014): 249-258.
    - **JOQUER**: Among patients with primary Sjögren syndrome, the use of hydroxychloroquine compared with placebo did not improve symptoms during 24 weeks of treatment. Further studies are needed to evaluate longer-term outcomes.

Osteoporosis:

- 1999: Pols, H. A. P., et al. "Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study." *Osteoporosis International* 9.5 (1999): 461-468.
    - **FOSIT** study: For postmenopausal women with low bone mass, alendronate is well tolerated and produces significant, progressive increases in BMD at the lumbar spine and hip in addition to significant reduction in the risk of nonvertebral fracture.
- 2006: Black, Dennis M., et al. "Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial." *Jama* 296.24 (2006): 2927-2938.
    - **FLEX**: Women who discontinued alendronate after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers but no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate. These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years.
- 2009: Brown, Jacques P., et al. "Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial." *Journal of Bone and Mineral Research* 24.1 (2009): 153-161.
    - Denosumab treatment led to significantly greater reduction of bone turnover markers compared with alendronate therapy. Adverse events and laboratory values were similar for denosumab- and alendronate-treated subjects. Denosumab showed significantly larger gains in BMD and greater reduction in bone turnover markers compared with alendronate. The overall safety profile was similar for both treatments.

- 2009: Saag, Kenneth G., et al. "Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: Thirty-six–month results of a randomized, double-blind, controlled trial." *Arthritis & Rheumatology* 60.11 (2009): 3346-3355.
    - Subjects with glucocorticoid-induced OP treated with teriparatide for 36 months had greater increases in BMD and fewer new vertebral fractures than subjects treated with alendronate.
- 2013: Tsai, Joy N., et al. "Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial." *The Lancet* 382.9886 (2013): 50-56.
    - **DATA** study: Combined teriparatide and denosumab increased BMD more than either agent alone and more than has been reported with approved therapies. Combination treatment might, therefore, be useful to treat patients at high risk of fracture.

Systemic JIA:

- 2011: Quartier, Pierre, et al. "A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial)." *Annals of the rheumatic diseases* 70.5 (2011): 747-754.
    - **ANAJIS**: Anakinra treatment is effective in SJIA, at least in the short term. It is associated with normalisation of blood gene expression profiles in clinical responders and induces a de novo IFN signature.

Giant Cell Arteritis:

- 2016: Villiger, Peter M., et al. "Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial." *The Lancet* 387.10031 (2016): 1921-1927.

- Our findings show, for the first time in a trial setting, the efficacy of tocilizumab in the induction and maintenance of remission in patients with giant cell arteritis.